# SYNTHESIS OF SOME HETEROCYCLIC NITROGEN COMPOUNDS

## I. TRIAZOLES II. PIPERIDINES

BY

JOHN CHAMBLIN LAWLER, JR.

B.S., Spring Hill College, 1938

M.S., University of Illinois, 1939

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY IN THE GRADUATE SCHOOL OF THE UNIVERSITY OF ILLINOIS, 1942

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## I. TRIAZOLES

### Introduction

For many years, the use of naturally occurring drugs, the alkaloids, to alleviate pain has been known. Morphine and the closely related codeine and heroin are analgesics of this type. Among common drugs having an effect on the heart (analeptics) may be mentioned camphor, caffeine, adrenaline, and the cardiac glycosides.

Recent studies have been made on the synthesis of derivatives of heterocyclic compounds to produce therapeutics of both these types. The heterocyclic rings studied were most often those containing carbon and nitrogen. Synthetic analgesics introduced are the barbiturates, Antipyrine, and Novocaine. Among the analeptic drugs brought out by synthetic studies are Cardiazole (Metrazole), Coramine, and Cycliton.

The purpose of the present work was to develop satisfactory methods for the synthesis of 1,2,3-triazole derivatives which could be studied as analgesics or analeptics. It was desirable to have an amine grouping to aid in solubility and the dialkylamide grouping to aid in therapeutic value.

### Experimental and Discussion

Para-nitrotriazobenzene was prepared from *p*-nitrophenylhydrazine in a 76 per cent yield by the action of nitrous acid.

Condensation of the azide with ethyl acetoacetate was effected by sodium in dry benzene to give 1-*p*-nitrophenyl-5-methyl-4-carbethoxy-1,2,3-triazole. When sodium ethylate was used as a catalyst for the condensation, hydrolysis of the azide took place and hydrazoic acid was evolved.[1]

The ester was prepared by another method. Dimroth[2] condensed triazobenzene with ethyl acetoacetate and hydrolyzed

the resulting ester to give 1-phenyl-5-methyl-1,2,3-triazole-4-carboxylic acid. The acid was treated with thionyl chloride followed by ethanol to give the ester. The latter was treated with fuming nitric acid, the nitro group entering the para position.

The ester was hydrolyzed most easily using diethylene glycol as a solvent. Treatment with thionyl chloride gave the acid chloride in poor yield. The competing reaction was the formation of the acid anhydride. Condensation with diethyl amine gave the N,N-diethyl amide in an 82 per cent yield.

The best method of preparing the nitrophenyl triazoles is shown as follows: triazobenzene → 1-phenyl-5-methyl-1,2,3-triazole-4-carboxylic acid → acid chloride → N,N-dialkyl-amides → *p*-nitrophenyl-5-methyl-1,2,3-triazole-4-(N,N-dialkyl)-carboxamides. The alkyl groups were methyl, ethyl, *n*-propyl, *n*-butyl, and *iso*-butyl.

Reduction of the nitro group in these compounds in strong acid solution resulted in hydrolysis of the amide. Reduction was accomplished in very dilute hydrochloric acid solution using iron powder. The corresponding free amines were formed in yields of 54-93 per cent.

## Summary

Para-nitro-triazobenzene was prepared in a 76 per cent yield by the diazotization of *p*-nitro-phenylhydrazine. It was condensed with ethyl acetoacetate and hydrolyzed to give 1-*p*-nitrophenyl-5-methyl-1,2,3-triazole-4-carboxylic acid. This was converted to the acid chloride by means of thionyl chloride. Treatment of the acid chloride with diethyl amine gave the corresponding N,N-diethylamide. The same amide and similar derivatives of other secondary amines were also made by nitration of 1-phenyl-5-methyl-1,2,3-triazole-4-(N, N-dialkyl-carboxamides.

The nitro compounds were reduced with iron and hydrochloric acid to give the corresponding amines in 54-93 per cent yields.

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## II. PIPERIDINES

### Introduction

Extensive studies have been made on the useful drug, morphine, to learn the effects of the individual groups and to find what part the natural arrangement of its groups plays in its activity.

The partially reduced phenanthrene ring and the piperidine ring both occur in morphine. They are usually physiologically active in all their derivatives. The phenanthrene ring also appears in the apomorphine and thebain alkaloids, while the piperidine ring appears in coniine, cocaine, and the lupine alkaloids.

The recent availability of phenanthrene and piperidine derivatives has facilitated the preparation of compounds containing these two rings.

It was desired to synthesize N-methyl-4-(9,10-dihydro-9-phenanthryl)-piperidine in order to test the physiological activity of this molecule which contains four of the ring systems present in morphine.

### Experimental and Discussion

N-Methyl-4-piperidone hydrochloride[1] was prepared by a Dieckmann ring closure on bis-($\beta$-carbethoxyethyl)-methylamine[2] followed by hydrolysis and loss of carbon dioxide. Purification of the free base by distillation resulted in a large amount of polymerization even at low temperatures under diminished pressure.

N-Methyl-4-hydroxy-4-(9-phenanthryl)-piperidine was prepared by the addition of 9-phenanthryl magnesium bromide[3] to N-methyl-4-piperidone. The yields were as high as 44 per cent when the piperidone was freshly distilled. When a benzene or ether extract of the ketone was used, the yields varied from 15-18 per cent. The low yields were undoubtedly due to the competing enolization reaction since an appreciable amount of phenanthrene was isolated.

The carbinol was dehydrated with glacial acetic acid by heating for 24 hours to give N-methyl-4-(9-phenanthryl)-$\triangle^3$-

tetrahydropyridine in 80-83 per cent yields.

Reduction was accomplished with hydrogen over Raney nickel at 100°. Two moles of hydrogen was absorbed to give N - methyl-4- (9,10-dihydro-9-phenanthryl) -piperidine, which was isolated both as the picrate and the hydrochloride.

## Summary

N - Methyl-4-hydroxy-4- (9-phenanthryl) -piperidine was prepared in a 44 per cent yield by the addition of 9-phenanthryl magnesium bromide to N-methyl-4-piperidone. The carbinol was dehydrated in 80-83 per cent yields to give N-methyl-4- (9-phenanthryl) -$\triangle^3$-tetrahydropyridine. N-Methyl-4- (9,10-dihydro-9-phenanthryl) -piperidine resulted when the terahydropyridine was reduced over Raney nickel at 100°C.

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## Vita

The author was born in Mobile, Alabama on June 30, 1917. He attended public and parochial schools in that city and was graduated from McGill Institute in 1934. In the fall of 1934, he entered Spring Hill College, Spring Hill, Alabama and received the degree of Bachelor of Science in June, 1938. He entered the Graduate School of the University off Illinois in the fall of 1938 as a Scholar for the year 1938-1939. He received the Master of Science degree in June, 1939. He was an Assistant in Inorganic and Organic Chemistry during the school year 1941-1942.

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